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(71) Applicant (for all designated States except US): **EURO-CELTIQUE S.A.** [LU/LU]; 122, Boulevard de la Petrusse, L-2330 Luxembourg (LU).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **REIDENBERG, Bruce, E.** [US/US]; 1 Stonycrest Road, Rye, NY 10580 (US). **SPYKER, Daniel, A.** [US/US]; 1520 Ralston Avenue, Burlingame, CA 94010 (US).

(74) Agents: **ROBINSON, Joseph, R.** et al.; Darby & Darby P.C., P.O. Box 5257, New York, NY 10150-5257 (US).

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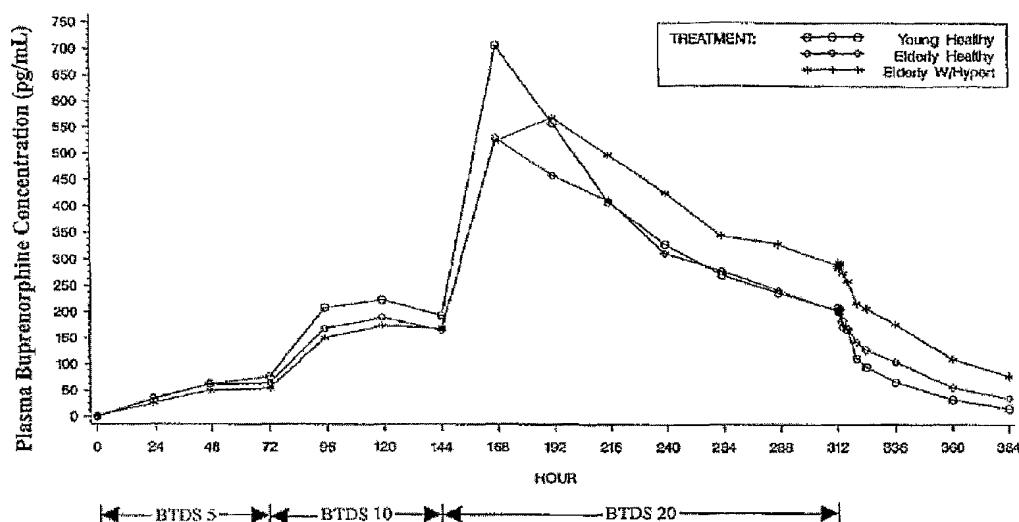
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(54) Title: TRANSDERMAL BUPRENORPHINE DOSAGE REGIMEN FOR TREATMENT OF DIARRHEA



(57) Abstract: A buprenorphine transdermal dosage regimen is provided that reduces symptoms such as pain and/or diarrhea are effectively reduced in patients suffering from one or more gastrointestinal conditions. The dosage regimen reduces the severity of breakthrough symptoms in a patient treated for symptoms of diarrhea. The gastrointestinal conditions include irritable bowel syndrome (IBS), short gut syndrome, microscopic colitis, and diarrhea associated with VIP-secreting carcinoids.

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Transdermal Buprenorphine Dosage Regimen For Treatment of Diarrhea

5 This application claims priority from U.S. Provisional Application No. 60/471,480, filed May 15, 2003, which is hereby incorporated by reference in its entirety.

FIELD OF THE INVENTION

The present invention relates to dosage regimens for controlling the symptoms of gastrointestinal conditions or disorders, including diarrhea and/or pain associated with the
10 conditions. The invention relates in particular to treating diarrhea associated with irritable bowel syndrome, short gut syndrome, microscopic colitis, and vasoactive intestinal polypeptide carcinoids.

BACKGROUND OF THE INVENTION

Approximately 5-10% of the U.S. population suffers from chronic diarrhea for
15 which an organic cause cannot be identified (Camilleri et al., Aliment Pharmacol Ther. 1977, 11:3-15; Talley et al., Gastroenterology 1991, 101:927-934). The diarrhea may be persistent or may alternate with periods of normal bowel habit or with periods of constipation. Chronic diarrhea, which is not accompanied by abdominal pain and which is not attributable to an organic cause, is referred to as "functional diarrhea" or "chronic
20 idiopathic diarrhea" (Drossman et al., Gastroenterology 1997, 112:2120-2137; Hasler et al., In: Textbook of Gastroenterology, 2nd ed. 1995, Yamada, Ed., J. B. Lippincott Co., Philadelphia, pp. 1832-1855; Camilleri et al., supra; Drossman et al., The functional Gastrointestinal disorders: Diagnosis, Pathophysiology, and Treatment, 1994, Degnon and Associates, McLean, Va.; Thompson et al., Gastroenterol. Intl. 1992, 5:75-91). Chronic
25 diarrhea, which is associated with abdominal pain and which is not attributable to an organic cause, is referred to as "irritable bowel syndrome with a diarrhea predominance" (Hasler et al., supra; American Gastroenterological Association, Gastroenterol. 1997,

112:2118-2119; Drossman et al., Gastroenterol. 1997, 112:2120-2137; Camilleri et al., *supra*).

Irritable bowel syndrome (IBS), estimated to affect up to 20% of the adult population worldwide, is a functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit. Other examples of gastrointestinal conditions are microscopic colitis, in which the patients suffer from non-bloody, chronic secretory diarrhea believed to be associated with inflammation of the colon; short bowel syndrome, a group of problems affecting people who have had half or more of their small intestine removed; and elevated VIP (vasoactive intestinal polypeptide) plasma levels in the “VIPoma” syndrome, which leads to intestinal secretion with severe secretory diarrhea (Krejs, Am J Med 1987, 29;82(5B):37-48).

Previous treatments for chronic diarrhea include restrictive diets, administration of fiber, loperamide, diphenoxylate, other opiates, anticholinergics, antispasmodics, cholestyramine, tricyclic and serotonin reuptake inhibitor antidepressants, sedatives, and psychological therapy. Anticholinergic agents can also be used to reduce intestinal motility. For treating microscopic colitis, anti-inflammatory agents and anti-diarrheal medications such as Imodium and Lomotil are commonly administered to delay diarrhea. In addition, prednisone (a corticosteroid) or antibiotics can be useful in stopping a severe attack, and anticholinergics and smooth muscle relaxants, such as cimetropium bromide, pinaverium bromide, octilium bromide, trimebutine, and mebeverine, while not directly leading to relief of abdominal pain in conditions such as IBS, can also relieve diarrhea.

Endogenous and exogenous opioid receptor ligands are known to modify and normalize gut function (Shook et al., J Pharmacol Exp Ther 1989;249:83-90; Corazzi, Can J Gastroenterol 1999;13:71A-75A), and several opioids such as loperamide, diphenoxylate, and codeine phosphate, have been shown useful in treating diarrhea. One particular opioid, buprenorphine is a potent, partial agonist of the μ -opioid receptor that has been shown to be effective to control pain in a wide range of patients when delivered by a number of different routes of administration, including intravenously, epidurally, intrathecally, or sublingually in both young and elderly patients (Inagaki et al., Anesth Analg 1996, 83:530-536; Brema et al., Int J Clin Pharmacol Res 1996, 16:109-116; Capogna et al., Anaesthesia 1988,

43:128-130; Adrianensen et al., Acta Anaesthesiol Belg 1985, 36:33-40; Tauzin-Fin et al., Eur J Anaesthesiol 1998, 15:147-152; Nasar et al., Curr Med Res Opin 1986, 10:251-255).

Despite advances in the art, there remains a need for methods of effectively treating patients suffering from diarrhea and/or abdominal pain resulting from conditions associated with diarrhea, especially in the context of preventing recurrent or breakthrough symptoms. These concerns are particularly acute with respect to providing a safe and effective method of symptom management in individuals suffering from irritable bowel syndrome, short gut syndrome, microscopic colitis, VIP carcinoids, and other gastrointestinal conditions.

SUMMARY OF THE INVENTION

The present invention provides a method for administering buprenorphine transdermal patches so that breakthrough symptoms such as pain and/or diarrhea are effectively reduced in patients suffering from one or more gut-related diseases or disorders, without substantially increasing the incidence of adverse side effects.

Accordingly, the invention provides a method of treating breakthrough symptoms of diarrhea in a patient comprising administering to the patient (1) a first buprenorphine-containing transdermal dosage form for a first dosing period that is no more than 5 days; (2) a second buprenorphine-containing transdermal dosage form for a second dosing period that is no more than 5 days, the second dosage form comprising the same dosage of buprenorphine as, or a greater dosage of buprenorphine than, the first dosage form; and (3) a third buprenorphine-containing transdermal dosage form for a third dosing period, the third dosage form comprising a greater dosage of buprenorphine than the second dosage form.

In specific embodiments, the first, second, and third transdermal dosage forms, respectively, contain approximately the amounts of buprenorphine set forth in a row in the following table:

<u>First (mg)</u>	<u>Second (mg)</u>	<u>Third (mg)</u>
5	5	10
5	5	20
5	5	30
5	10	20
5	10	30
5	10	40
5	20	40
5	30	40
10	10	20
10	10	30
10	10	40
10	20	30
10	20	40
10	30	40
20	20	30
20	20	40
20	30	40

Preferably, the first, second, and third dosing periods are each at least 2 days.

More preferably, the first and/or second dosing periods are 7 days, 5 days, 4 days or 3 days. In a specific embodiment, the first dosage period is 2 days. In another embodiment, the second dosage period is 2 or 3 days. In yet another embodiment, the first, second, and third dosage periods are each 7 days. Optionally, the method of the invention further comprises administering a fourth buprenorphine-containing transdermal dosage form for a fourth dosage period after the third dosing period. For example, the fourth dosing period could be 2 days, and the fourth dosage form could comprise 30 or 40 mg buprenorphine. If needed, additional buprenorphine-containing dosage forms may be administered, preferably sequentially, after the fourth dosing period. In one embodiment, these additional dosage forms contain about the same dose as the third or fourth dosage form.

In one embodiment, the first dosage form comprises 5 mg of buprenorphine. In another embodiment, the second dosage form comprises 10 mg of buprenorphine. In yet other embodiments, the third dosage form comprises 20, 30, or 40 mg of buprenorphine, and the subsequent dosage form comprises 30 or 40 mg of buprenorphine. One preferred
5 embodiment is where the first dosage form comprises up to 5 mg of buprenorphine, for a dosing period up to 3 days, the second dosage form comprises up to 5 mg of buprenorphine, for a dosing period up to 3 days, and the third dosage form comprises up to 20 mg of buprenorphine, the third dosing period lasting up to 7 days.

In particular embodiments, the patients are pediatric or elderly, suffering from
10 breakthrough symptoms of diarrhea. Conditions where breakthrough symptoms of diarrhea may occur include, but are not limited to, those wherein the patient is suffering from irritable bowel syndrome, short gut syndrome, microscopic colitis, or carcinoid tumor secreting VIP. Preferably, the breakthrough symptoms include, but are not limited to abnormally loose or liquid feces, or abnormally frequent emptying of the bowels and
15 cramping abdominal pain.

The invention also provides a method of treating breakthrough diarrhea symptoms in a patient in need thereof, by administering a first, a second, and a third transdermal dosage form of buprenorphine, wherein the third dosage form comprises a higher dosage of
20 buprenorphine than the first and second dosage forms, and wherein the method does not increase the incidence of an adverse event selected from nausea, vomiting, and headache as compared to only administering the same dosage of buprenorphine as the third dosage form. In one embodiment, the first dosage form comprises no more than 5, 10, or 20 mg buprenorphine, the second dosage form comprises no more than 10, 20, or 30 mg buprenorphine and is administered for 3 days, and the third dosage form comprises at least
25 20, 30, or 40 mg buprenorphine and is administered for at least 2 days. The transdermal administration can be produced by a transdermal system selected from a skin patch, a topical gel, a lotion, an ointment, a transmucosal system, a transmucosal device, and an iontophoretic delivery system.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. Plasma concentration versus time curves for buprenorphine after application of BTDS 5 (hours 0-72), BTDS 10 (hours 72-144), and BTDS 20 (hours 144-312).

5 **Figure 2.** Plasma concentration versus time curves for norbuprenorphine after application of BTDS 5 (hours 0-72), BTDS 10 (hours 72-144), and BTDS 20 (hours 144-312).

DETAILED DESCRIPTION OF THE INVENTION

10 The present invention provides a method of more quickly achieving effective treatment of symptoms such as pain and diarrhea in a patient in need of such treatment, while reducing the incidence of certain adverse effects.

The method comprises administering to the patient an effective amount of buprenorphine in a series of transdermal dosage forms of buprenorphine. The dosage regimen of the present invention yields important advantages over prior art dosage
15 regimens for opioids in that it is a promising short-term and long-term treatment for controlling diarrhea as well as pain. The present invention provides effective therapy for patients in need of such treatment, including but not limited to those individuals suffering from IBS, short gut syndrome, microscopic colitis, and VIP.

Known methods for reducing the incidence or severity of diarrhea usually relies on
20 frequent administration of oral medications to treat the diarrhea. A problem with such regimens is, however, that the patient may suffer from breakthrough symptoms if even a single dose is missed. In contrast, the present invention provides a sustained-release dosage form that avoids any breakthrough symptoms through the mode of administration. The method also increases the degree of patient compliance with drug therapy and treatment
25 efficacy. Notably, the reduction in side effects and minimization of complications does not diminish the primary therapeutic effect: control of diarrhea.

As used herein, “symptoms of diarrhea” include, but are not limited to, abnormally soft or liquid feces, abnormally frequent emptying of bowels and cramping abdominal pain.

As used herein, “breakthrough symptoms” refer to a situation where a patient treated for prolonged symptoms of diarrhea, using repeated doses of an orally or
5 parenterally administered medicament, suffers from the return of symptoms of diarrhea. This may be caused by, for example, the patient missing a dose, or any other unforeseen event leading to reduced efficacy of the treatment, thereby leading to breakthrough symptoms.

The dosage regimen of the present invention may alternatively be described in terms
10 of administration of a “series of transdermal dosage forms comprising at least one incremental dosage of buprenorphine”. This refers to the application of at least two transdermal dosage forms to the patient, wherein at least one subsequently administered dosage form has a greater dosage of buprenorphine than the previous dosage form. For example, a series of three transdermal dosage forms may be administered in the dosage
15 regimen, wherein the first dosage form contains 5 mg buprenorphine, the second dosage form contains 10 mg buprenorphine, and the third dosage form contains 20 mg buprenorphine, such that each subsequent dosage form in the series has twice the dosage of buprenorphine than its predecessor. Alternatively, the series of dosage forms may include 20 mg, 30 mg, and 40 mg buprenorphine respectively, or 2 mg, 4 mg, and 8 mg
20 buprenorphine, respectively, or 1 mg, 2 mg, or 3 mg buprenorphine, respectively. Particular dosage regimens (in mg) are 5-5-10, 5-10-10, 5-10-20, 5-20-40, 5-10-30, 5-30-40, 10-10-20, 10-10-30, 10-10-40, 10-20-30, 10-20-40, and 10-30-40.

As used herein, “BTDS” means “Buprenorphine Transdermal System”, and “BTDS X”, wherein “X” is a number higher than zero, means a transdermal dosage form
25 containing X milligrams of buprenorphine. Thus, “BTDS 5” means a transdermal system containing 5 mg buprenorphine. Preferably, a BTDS contains buprenorphine in the form of a base or a salt, more preferably in the form of a base.

The term “relative release rate,” “flux rate,” or “delivery rate” is determined from the amount of drug released per unit time from a transdermal delivery system through the

skin and into the bloodstream of a subject. Mean relative release rate may be expressed, *e.g.*, as $\mu\text{g drug/hr}$ or, for comparing delivery systems covering skin areas of different size, as $\mu\text{g drug/cm}^2/\text{hr}$. For example, a transdermal delivery system that releases 1.2 mg of buprenorphine over a time period of 72 hours is considered to have a relative release rate of
5 16.67 $\mu\text{g/hr}$. For purposes of the invention, it is understood that relative release rates may change between any particular time points within a particular dosing interval, and the term therefore only reflects the overall release rate during the particular dosing interval.

In a preferred embodiment, the dose of buprenorphine administered to the patient is gradually escalated to a predetermined level, and the reduction in symptoms of the
10 gastrointestinal condition assessed. If additional reduction in symptoms is desired, the dose of buprenorphine administered to the patient can be further escalated until any pain and/or diarrhea symptoms exhibited or experienced by the patient have been sufficiently reduced. For example, control of diarrhea in an IBS patient can be achieved, *e.g.*, by escalating the buprenorphine dosage to an effective dose, preferably BTDS 20. Likewise, control of
15 cramping abdominal pain in an IBS patient can be achieved, *e.g.*, by escalating the buprenorphine dosage to an effective dose, preferably BTDS 20. Preferably, effective pain relief is achieved without increasing adverse events such as, for example, nausea. In general, when applying buprenorphine transdermal dosage forms, the physician in charge of the patient's care determines the BTDS level suitable for controlling symptoms of
20 diarrhea and/or pain. As discussed below, the invention further provides kits containing the desired dosage series.

The method of the present invention may be administered to any patient in need of control of diarrhea and/or pain. The patient may be in the elderly (age over 65 years), young adult (age between 18 and 45 years), or pediatric (age between birth and 17 years)
25 population, and is preferably, although not necessarily, classified as suffering from or having a gastrointestinal condition. In the context of the invention the term "gastrointestinal condition" means that the patient suffers from an existing condition having diarrhea as a major symptom, optionally diarrhea associated with pain. Such conditions include IBS, short gut syndrome, microscopic colitis, and VIP (carcinoid).

The patient may be classified as, but need not be, an at risk patient. In the context of the invention, the term “at risk” means that the patient suffers from an existing condition that is a relative contraindication for high-dose opioid therapy or intermittent-opioid therapy or increases the likelihood of adverse events from such therapy. Such conditions include age or respiratory compromise, for instance due to recurrent bronchospasm. At risk populations include the elderly and pediatric populations.

As used herein, the term “predefined number of days” refers to a predetermined length of time during which the dosage form of the drug is administered to the patient. Preferably, the drug is an opioid and more preferably the opioid is buprenorphine. The predefined number of days may vary between individuals and may be determined by one of ordinary skill in the art using the guidelines discussed within the present application. In one embodiment, the predefined number of days is three days. In another embodiment, the predefined number of days is seven days.

An “analgesically effective” amount of an analgesic agent means an amount of agent capable of lowering the level of pain experienced by a patient. The level of pain experienced by a patient can be assessed by use of a visual analog scale (VAS) or a Likert-type scale. A VAS is a straight line with one end of the line representing no pain and the other end of the line representing the worst imaginable pain. Patients are asked to mark on the line where they considered their pain to be at each time point, and the length from no pain to the mark can be related to the length of the full scale. A Likert-type scale is a rating scale, usually in the range of 1 to 5, based on degrees of agreement or disagreement to statements. A similar type of scale, although based on an 11 point scale (ranging from 0 to 10) can also be used. Such pain scales can be applied to visualize an alteration of the level of pain a patient experiences during treatment, *e.g.*, a reduction of the level of pain a patient or a population of patients experiences before and after initiation of a pain therapy.

Buprenorphine

The present invention relates to buprenorphine or a pharmaceutically acceptable salt, ether derivative, ester derivative, acid derivative, enantiomer, diastereomer, racemate, polymorph, or solvate thereof. Pharmacologically, without being bound to any particular theory, buprenorphine is considered in the art to be a partial agonist at μ opioid receptors in

the central nervous system ("CNS") and peripheral tissues. Buprenorphine shares many of its actions, such as analgesia, of full μ opioid agonists. Partial agonists, generally, include compounds with affinity for a receptor, but unlike full agonists, elicit an incomplete degree of the pharmacological effect, even if a high proportion of receptors are occupied by the compound. A "ceiling effect" to analgesia (*i.e.*, no additional analgesia with increasing dose) is well documented with respect to buprenorphine in many animal models. It is highly lipophilic and dissociates slowly from opioid receptors. It is further thought that buprenorphine binds with high affinity to μ and κ receptors, and, with lower affinity, to δ receptors. The intrinsic agonist activity at the κ receptor seems to be limited and most evidence suggests that buprenorphine has antagonist activity at σ receptors. The lack of σ agonism accounts for buprenorphine's apparent lower incidence of the dysphoric and psychotomimetic effects that can be seen with κ agonist opioid drugs (such as pentazocine). Other studies suggest that the opioid antagonist effects of buprenorphine may be mediated via an interaction with σ opioid receptors.

Buprenorphine is believed to bind slowly with, and dissociate slowly from, the σ receptor. The high affinity of buprenorphine for the σ receptor and its slow binding to, and dissociation from, the receptor is thought to possibly account for the prolonged duration of analgesia and, in part, for the limited physical dependence potential observed with the drug. The high affinity binding may also account for the fact that buprenorphine can block the σ agonist effects of other administered opioids.

Like other opioid agonists, buprenorphine produces dose-related analgesia. The exact mechanism has not been fully explained, but analgesia appears to result from a high affinity of buprenorphine for μ and possibly κ opioid receptors in the central nervous system. The drug may also alter the pain threshold (threshold of afferent nerve endings to noxious stimuli). On a weight basis, the analgesic potency of parenteral buprenorphine appears to be about 25 to about 50 times that of parenteral morphine, about 200 times that of pentazocine, and about 600 times that of meperidine.

Salts and Derivatives

Use of various pharmaceutically acceptable salts, ether derivatives, ester derivatives, acid derivatives, and aqueous solubility altering derivatives of the active

compound also are encompassed by the present invention. The present invention further includes the use of all active individual enantiomers, diastereomers, racemates, and other isomers of the compound. The invention also includes the use of all polymorphs and solvates, such as hydrates and those formed with organic solvents, of this compound. Such isomers, polymorphs, and solvates may be prepared by methods known in the art, such as by regiospecific and/or enantioselective synthesis and resolution.

Suitable salts of the compound include, but are not limited to, acid addition salts, such as those made with hydrochloric, hydrobromic, hydroiodic, perchloric, sulfuric, nitric, phosphoric, acetic, propionic, glycolic, lactic pyruvic, malonic, succinic, maleic, fumaric, malic, tartaric, citric, benzoic, carbonic cinnamic, mandelic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzenesulfonic, p-toluene sulfonic, cyclohexanesulfamic, salicylic, p-aminosalicylic, 2-phenoxybenzoic, and 2-acetoxybenzoic acid; salts made with saccharin; alkali metal salts, such as sodium and potassium salts; alkaline earth metal salts, such as calcium and magnesium salts; and salts formed with organic or inorganic ligands, such as quaternary ammonium salts.

Additional suitable salts include, but are not limited to, acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate salts of the compound.

The present invention includes the use of prodrugs of the compound. Prodrugs include, but are not limited to, functional derivatives of buprenorphine that are readily convertible *in vivo* into buprenorphine. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

Transdermal Dosage Forms

Transdermal dosage forms are convenient dosage forms for delivering many different active therapeutically effective agents, including but not limited to analgesics, such as for example, opioid analgesics. Typical opioid analgesics include, but are not limited to, fentanyl, buprenorphine, etorphines, and other high potency narcotics. Transdermal dosage forms are particularly useful for timed release or sustained release of active agents.

Transdermal dosage forms may be classified into transdermal dosage articles and transdermal dosage compositions. The most common transdermal dosage article is a diffusion-driven transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system. Transdermal dosage compositions include, but are not limited to, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery systems. Preferably, the transdermal dosage form is a transdermal patch.

The pharmaceutical compositions are formulated as transdermal dosage forms, such as a diffusion-driven transdermal system (transdermal patch) using either a fluid reservoir or a drug-in-adhesive matrix system, topical gels, lotions, ointments, transmucosal systems and devices, and iontophoretic (electrical diffusion) delivery system. The transdermal dosage form is used in the dosage regimen of the present invention for timed release or sustained release of buprenorphine.

Transdermal dosage forms used in accordance with the invention preferably include a backing layer made of a pharmaceutically acceptable material which is impermeable to the buprenorphine. The backing layer preferably serves as a protective cover for the buprenorphine, and may also provide a support function. Examples of materials suitable for making the backing layer are films of high and low density polyethylene, polypropylene, polyvinylchloride, polyurethane, polyesters such as poly(ethylene phthalate), metal foils, metal foil laminates of such suitable polymer films, textile fabrics, if the components of the reservoir cannot penetrate the fabric due to their physical properties, and the like.

Preferably, the materials used for the backing layer are laminates of such polymer films with a metal foil such as aluminum foil. The backing layer can be any appropriate thickness to provide the desired protective and support functions. A suitable thickness will be from

about 10 to about 200 microns. Desirable materials and thickness will be apparent to the skilled artisan.

In certain preferred embodiments, the transdermal dosage forms used in accordance with the invention contain a pharmacologically or biologically acceptable polymer matrix layer. Generally, the polymers used to form the polymer matrix are those capable of forming thin walls or coatings through which pharmaceuticals can pass at a controlled rate. A non-limiting list of exemplary materials for inclusion in the polymer matrix includes polyethylene, polypropylene, ethylene/propylene copolymers, ethylene/ethylacrylate copolymers, ethylenevinyl acetate copolymers, silicones, rubber, rubber-like synthetic homo-, co- or block polymers, polyacrylic esters and the copolymers thereof, polyurethanes, polyisobutylene, chlorinated polyethylene, polyvinylchloride, vinyl chloride-vinyl acetate copolymer, polymethacrylate polymer (hydrogel), polyvinylidene chloride, poly(ethylene terephthalate), ethylene-vinyl alcohol copolymer, ethylene-vinyloxyethanol copolymer, silicones including silicone copolymers such as polysiloxane-polymethacrylate copolymers, cellulose polymers (*e.g.*, ethyl cellulose, and cellulose esters), polycarbonates, polytetrafluoroethylene and mixtures thereof. Exemplary materials for inclusion in the polymer matrix layer are silicone elastomers of the general polydimethylsiloxane structures, (*e.g.*, silicone polymers). Preferred silicone polymers cross-link and are pharmaceutically or biologically acceptable. Other preferred materials for inclusion in the polymer matrix layer include: silicone polymers that are cross-linkable copolymers having dimethyl and/or dimethylvinyl siloxane units that can be crosslinked using a suitable peroxide catalyst. Also preferred are those polymers consisting of block copolymers based on styrene and 1,3-dienes (particularly linear styrene-isoprene-block copolymers of styrene-butadiene-block copolymers), polyisobutylenes, polymers based on acrylate and/or methacrylate.

The polymer matrix layer may optionally include a pharmaceutically acceptable crosslinking agent. Suitable crosslinking agents include, *e.g.*, tetrapropoxy silane. Preferred transdermal delivery systems used in accordance with the methods of the present invention include an adhesive layer to affix the dosage form to the skin of the patient for the desired period of administration. If the adhesive layer of the dosage form fails to provide adhesion for the desired period of time, it is possible to maintain contact between the

dosage form with the skin by, for instance, affixing the dosage form to the skin of the patient with an adhesive tape, *e.g.*, surgical tape.

The adhesive layer preferably includes using any adhesive known in the art that is pharmaceutically compatible with the dosage form and preferably hypoallergenic, such as polyacrylic adhesive polymers, acrylate copolymers (*e.g.*, polyacrylate) and polyisobutylene adhesive polymers. In other preferred embodiments of the invention, the adhesive is a hypoallergenic and pressure-sensitive contact adhesive.

The transdermal dosage forms that can be used in accordance with the present invention may optionally include a permeation enhancing agent. Permeation enhancing agents are compounds that promote penetration and/or absorption of the buprenorphine through the skin or mucosa and into the blood stream of the patient. A non-limiting list of permeation enhancing agents includes polyethylene glycols, surfactants, and the like.

Alternatively, permeation of buprenorphine may be enhanced by occlusion of the dosage form after application to the desired site on the patient with, *e.g.* an occlusive bandage. Permeation may also be enhanced by removing hair from the application site by, *e.g.* clipping, shaving or use of a depilatory agent. Another permeation enhancer is heat. It is thought that permeation can be enhanced by, among other things, the use of a radiating heat form, such as an infrared lamp, at the application site during at least a portion of the time the transdermal dosage form is applied on the skin or mucosa. Other means of enhancing permeation of buprenorphine such as the use of iontophoretic means, are also contemplated to be within the scope of the present invention.

A preferred transdermal dosage form that may be used in accordance with the present invention includes a non-permeable backing layer made, for example, of polyester; an adhesive layer made, for example, of a polyacrylate, and a matrix containing the buprenorphine and other desirable pharmaceutical aids such as softeners, permeability enhancers, viscosity agents and the like.

The active agent, buprenorphine, may be included in the device in a drug reservoir, drug matrix or drug/adhesive layer. This area of the patch, and the amount of active agent

per unit area, determine the limit dose, as one of ordinary skill in the art can readily determine.

Certain preferred transdermal delivery systems also include a softening agent in the reservoir or matrix. Suitable softening agents include higher alcohols such as dodecanol, undecanol, octanol, esters of carboxylic acids, wherein the alcohol component may also be a polyethoxylated alcohol, diesters of dicarboxylic acids, such as di-n-butyladiapate, and triglycerides, particularly medium-chain triglycerides of caprylic/caproic acids or coconut oil. Further examples of suitable softeners are, for example, multivalent alcohols such as glycerol and 1,2-propanediol, as well as softeners such as levulinic acid and caprylic acid, which can also be esterified by polyethylene glycols.

A buprenorphine solvent may also be included in the transdermal delivery systems of the present invention. Preferably, a solvent dissolves the buprenorphine to a sufficient extent thereby avoiding complete salt formation. A non-limiting list of suitable solvents include those with at least one acidic group. Particularly suitable are monoesters of dicarboxylic acids such as monomethylglutarate and monomethyladipate.

Other pharmaceutically acceptable components that may be included in the reservoir or matrix include solvents, for example, alcohols such as isopropanol; permeation enhancing agents such as those described above; and viscosity agents, such as cellulose derivatives, natural or synthetic gums, such as guar gum, and the like.

In preferred embodiments, the transdermal dosage form includes a removable protective or protective release layer. The removable protective layer is removed prior to application, and may consist of the material used for the backing layer described above, provided that it is rendered removable, for example, by a silicone treatment. Other removable protective layers, for example, are polytetra-fluoroethylene, treated paper, allophane, polyvinyl chloride, and the like. Generally, the removable protective layer is in contact with the adhesive layer and provides a convenient means of maintaining the integrity of the adhesive layer until the desired time of application.

The composition of the transdermal dosage form used in accordance with the invention and the type of device used are not considered critical to the method of the invention, provided that the device delivers the active agent, *e.g.* buprenorphine, for the desired time period and at the desired flux or delivery rate, *i.e.*, the rate of penetration of the active agent through the skin of an individual, of the transdermal dosage form.

Several types of transdermal formulations of buprenorphine have been described. See, for example, U.S. Pat. No. 5,240,711 to Hille et al., U.S. Pat. No. 5,225,199 to Hidaka et al., U.S. Pat. No. 5,069,909 to Sharma et al., U.S. Pat. No. 4,806,341 to Chien et al.; U.S. Pat. No. 5,026,556 to Drust et al.; U.S. Pat. No. 5,613,958 to Kochinke et al.; and U.S. Patent No. 5,968,547 to Reder et al. Transdermal delivery systems of buprenorphine, made by Lohmann Therapie-Systeme GmbH & Co., are currently sold in the European Union under the trademark name TRANSTEC®. These patches contain 20, 30, and 40 mg of buprenorphine, with an approximate delivery or flux rate of 35, 52.5, and 70 µg/hr, respectively.

A preferred buprenorphine transdermal delivery system includes a laminated composite having an impermeable backing layer, and, optionally, a permeation enhancer, and a pressure-sensitive adhesive. For example, a transdermal dosage form in accordance with U.S. Patent No. 5,240,711 includes: (i) a polyester backing layer which is impermeable to buprenorphine; (ii) a polyacrylate adhesive layer; (iii) a separating polyester layer; and (iv) a matrix containing buprenorphine or a salt thereof, a solvent for the buprenorphine, a softener and a polyacrylate adhesive. The buprenorphine solvent may or may not be present in the final formulation. Preferably, the matrix includes about 10 to about 95% (by weight) polymeric material, about 0.1 to about 40% (by weight) softener, and about 0.1 to about 30% (by weight) buprenorphine. A solvent for the buprenorphine base or pharmaceutically acceptable salt thereof may be included as about 0.1 to about 30% (by weight).

The dosing regimen of the present invention comprises several discrete dosing periods. A dosing period is the time during which one of the transdermal dosage forms in the series is administered to the patient. Accordingly, the dosing regimen will consist of a separate dosing period for administration of each transdermal dosage form in the series.

Thus, for example, the first transdermal dosage form in the series may be worn by the patient for three consecutive days. Upon removal, the second dosage form may then be worn by the patient for another three consecutive days, and thereafter, the third dosage form may be worn by the patient for another seven days. In one embodiment of the dose escalation regimen, the third dosage form, corresponding to the third and final dosage level, is administered after six consecutive days of buprenorphine treatment. In another embodiment, the first dosage form is worn for seven days, the second dosage form for seven days, and the third dosage form for seven days, which means that the third dosage level is reached after 14 consecutive days of buprenorphine treatment. This dose can then be maintained for as long as needed, or indefinitely. If an increase in dosage is required, then the dosage may be increased at an appropriate interval, *e.g.*, every three or seven days.

The dosage forms of the present invention may also include one or more inactivating agents. The term "inactivating agent" refers to a compound that inactivates or crosslinks the active agent, in order to decrease the abuse potential of the transdermal dosage form. Non-limiting examples of a inactivating agents include, but are not limited to, polymerizing agents, photo-initiators, and formalin. Examples of crosslinking or polymerizing agents include diisocyanates, peroxides, diimides, diols, triols, epoxides, cyanoacrylates, and UV-activated monomers.

Any appropriate additives, inactivating agents, and dosage forms that are known in the art may be used in combination with the method of the invention.

The method of the present invention preferably comprises administering buprenorphine in a manner that achieves a rapid increase in the plasma concentration of buprenorphine in the patient. In preferred embodiments, the level of buprenorphine may be maintained indefinitely by the replacement of the set dosage level of the third patch every three or seven days.

Topical preparations typically contain a suspending agent and optionally, an antifoaming agent. Such topical preparations may be liquid drenches, alcoholic solutions,

topical cleansers, cleansing creams, skin gels, skin lotions, and shampoos in cream or gel formulations (including, but not limited to aqueous solutions and suspensions).

Alternatively, buprenorphine can be administered in the form of a liposome delivery system. For example, small unilamellar vesicles, large unilamellar vesicles and/or
5 multilamellar vesicles that may be included in the transdermal article or transdermal composition. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The transdermal dosage form may be formulated by any method known in the art and may be administered as suggested. Such formulations are described in U.S. Patents
10 4,806,341; 5,240,711; and 5,968,547.

Administration

The unit dosage forms of the present invention are administered to a patient, preferably a human patient, suffering from symptoms of diarrhea. The unit dosage forms of the present invention may be administered at the defined dosing regimen in order to
15 rapidly achieve optimal activity while reducing the incidence of any potential adverse effects. Such adverse effects may be, but are not limited to, nausea, vomiting, headache, dizziness, and somnolence.

The method of the invention preferably involves administering to the patient an analgesic effective amount of buprenorphine in a dosage regimen comprising a series of
20 transdermal dosage forms of graduated and ascending dosages of buprenorphine.

Preferably, the dosage regimen comprises administering to the patient:

- (a) a first buprenorphine-containing transdermal dosage form for a first dosing period;
- (b) a second buprenorphine-containing transdermal dosage form for a second
25 dosing period, wherein the second dosage form comprises the same or a greater dosage of buprenorphine than the first dosage form; and
- (c) a third buprenorphine-containing transdermal dosage form for a third dosing period, wherein the third dosage form comprises a greater dosage of buprenorphine than the second dosage form.

In a specific embodiment the first dosage form comprises up to 5 mg buprenorphine, and the first dosing period is at least about 2 days; the second dosage form comprises up to 10 mg buprenorphine, and the second dosing period is at least about 3 days; and the third dosage form comprises up to 20 mg buprenorphine, and the third dosing period is at least about 2 days. In another specific embodiment, the first and second dosing periods are no more than about 7 days each, preferably no more than about 5 days, and even more preferably no more than about 3 days. In yet another specific embodiment, the first, second, and third dosing periods are each about 7 days.

The method of the present invention preferably administers buprenorphine in a manner that achieves a gradual increase in the plasma concentration of buprenorphine in the patient. In a preferred embodiment, the plasma profile achieved by the method of the present invention may be described as certain plasma concentration values at specific time points ("t") after the dosage regimen is begun, as follows:

- (a) a mean plasma buprenorphine concentration at t=24 hours of between 10-100 pg/ml, preferably 20-50 pg/ml;
- (b) a mean plasma buprenorphine concentration at t=72 hours of between 25-200 pg/ml, preferably 40-100 pg/ml;
- (c) a mean plasma buprenorphine concentration at t=144 hours of between 100-250 pg/ml, preferably 150-200 pg/ml; and
- (d) a mean plasma buprenorphine concentration at t=168 hours after administration of between 400-1000 pg/ml, preferably at least 500 pg/ml, or higher depending on the patient's need.

In a preferred embodiment, the method of the present invention achieves a plasma profile that is substantially similar to that depicted in Figure 1. "Substantially similar" refers to a profile of which the maximum plasma concentration (c_{max}) or area under the plasma concentration-time course profile (AUC) differs by no more than 30% from that of at least one of the reference profiles depicted in Figure 1. Preferably, the maximum plasma concentration (c_{max}) and/or area under the plasma concentration-time course profile (AUC) differs no more than 20%, even more preferably no more than 10%, from that of a reference profile depicted in Figure 1. Alternatively, the plasma profile is bioequivalent to

the reference profile, as determined according to Food and Drug Administration (FDA) guidelines (see 21 C.F.R. §320, and "Guidance for Industry - Statistical Approaches to Establishing Bioequivalence" U.S. Dept. of Health and Human Services, FDA, and CDER, January 2001).

5 In another embodiment, subsequent dosages may be administered. For example, if the target analgesia level is attained with the third dosing period, fresh replacements of the third dosage form can be repeatedly administered for an extended period of time, changing patches with a frequency extending from about every 2 days to about weekly. If the target levels of analgesia and/or control of diarrhea are not attained within the third dosing period, 10 subsequent dosage forms, comprising incrementally increasing levels of buprenorphine, can be applied, starting with 30 mg buprenorphine and 40 mg buprenorphine load.

 The dosage of buprenorphine may vary according to a variety of factors such as underlying disease states, the individual's condition, weight, sex and age and the mode of administration. The dosage predefined interval or regimen is selected in accordance with a 15 variety of factors including species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the selected transdermal delivery system; the renal and hepatic function of the patient; and the particular form of buprenorphine used. A physician or veterinarian of ordinary skill will readily be able to determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the 20 condition in view of this disclosure. Optimal precision in achieving concentrations of drug within the range that yields efficacy without toxicity requires a regimen based on the kinetics of the drug's availability to target sites. This involves a consideration of the absorption, distribution, metabolism, and excretion of a drug.

 The composition or dosage form of the invention, when administered as a 25 transdermal dosage form, may be provided to any body part as determined by one of ordinary skill in the art. For example, the composition or dosage form may be provided to the arm, leg or chest of the patient. In the preferred embodiment for children, the placement is preferably on the back to prevent the removal of the transdermal unit. Repeated doses may or may not be administered to the same location each time. 30 Preferably, the dosages are administered to the same location.

Generally, topical preparations contain from about 0.01 to about 100% by weight and preferably from about 3 to about 80% by weight of buprenorphine, based upon 100% total weight of the topical preparation. Generally, transdermal dosage forms contain from about 0.01 to about 100% by weight and preferably from about 3 to about 50% by weight of the compound, based upon 100% total weight of the buprenorphine formulation in the dosage form.

The dosage forms used in the method of the present invention may be administered alone or in combination with other active agents. For combination treatment with more than one active agent, where the active agents are in separate dosage formulations, the active agents can be administered concurrently, or they each can be administered at separately staggered times. The dosage amount may be adjusted when combined with other active agents as described above to achieve desired effects. Alternatively, unit dosage forms of these various active agents may be independently optimized and combined to achieve a synergistic result wherein the pathology is reduced more than it would be if either active agent were used alone.

Kits

The present invention also provides an embodiment wherein the components for practicing the invention can be conveniently provided in a kit form. In its simplest embodiment, a kit of the invention provides a set number of buprenorphine patches at set dosages, wherein the dosages are set according to the needs of the patient. Each kit will include the appropriate dosage regimen selected from the following table.

Amount of Buprenorphine per Transdermal Dosage Form (mg)		
First	Second	Third
5	5	10
5	5	20
5	5	30
5	10	20
5	10	30
5	10	40

5	20	40
5	30	40
10	10	20
10	10	30
10	10	40
10	20	30
10	20	40
10	30	40
20	20	30
20	20	40
20	30	40

In a preferred embodiment, the dosage regimen is 5 mg, 10 mg, and 20 mg.

Printed instructions on how to apply the patch, storage of the unit, and details of the treatment regimen may also be included. For example, the printed instructions may describe the use of the dosage regimen to treat or prevent diarrhea or other gastrointestinal conditions or disorders. A kit according to the invention preferably includes packaging and instructions for its use, *e.g.*, on the packaging or package insert. The buprenorphine patches within the kit may also be coded (*i.e.*, color, numerical by day, or numerical by dose, etc.) for the patient.

In a further embodiment, the kit will include a disposal container or device for disposal of used buprenorphine patches. Any such containers or devices known in the art can be used to prevent or limit potential abuse of the drug within the patch. As used herein, the term container has its broadest meaning; *i.e.*, any receptacle for holding material.

EXAMPLES

The present invention will be better understood by reference to the following Examples, which are provided as exemplary of the invention, and not by way of limitation.

EXAMPLE 1: Physiologic effects of BTDS dosing regimen

This example evaluates the physiologic effects of BTDS dose escalation in young and elderly subjects.

5

Subjects

Young healthy subjects: male or female subjects, aged 21-40 years, body weight ranging from 70-94 kg (males) and 55 to 81 kg (females). Patients were free of significant abnormal medical history, as evidenced by baseline physical examination, hematology, blood chemistries, urinalysis, ECG, and vital signs. Females had to have a negative serum pregnancy testing during screening visit and at predose. Barrier or IUD contraception with additional spermicidal foam or jelly was to be used from screening until discharge from the study.

Elderly healthy subjects: male or female elderly subjects, aged 65-74 years, inclusive, body weight ranging from 70-94 kg (males) and 55 to 81 kg (females). Patients were free of significant abnormal medical history, as evidenced by baseline physical examination, hematology, blood chemistries, urinalysis, ECG, and vital signs. Females had to be postmenopausal, *i.e.*, at least one year without menses, or surgically sterile. A certain group of elderly patients suffered from hypertension (see data below).

Exclusion Criteria

20

1. Any history of hypersensitivity to opioids or to psychotropic or hypnotic drugs.

2. History of seizures, presyncope, or syncope.

25

3. Any medical or surgical conditions that might significantly interfere with transdermal absorption, distribution, metabolism or excretion of buprenorphine.

4. Any concomitant medical conditions requiring ongoing prescription or over-the-counter medication, except for hormone replacement therapy (systemic

or local) in elderly female subjects and antihypertensive medications in elderly hypertensive subjects.

5. Use of opioid-containing medication for more than 7 days within past 3 months.

5 6. History of drug or alcohol abuse in the past 2 years.

7. Documented, ongoing, clinically significant cardiovascular, pulmonary, endocrine, neurologic, metabolic, or psychiatric disease.

8. History of frequent nausea or emesis regardless of etiology.

10 9. Participation in a clinical study during the 30 days prior to enrollment in this study.

10. Any significant illness during the 4 weeks preceding entry into this study.

11. Use of any medication, including vitamin and/or mineral supplements, during the 7 days preceding study medication application.

15 12. Refusal to abstain from food and caffeine-containing beverages from 8 hours preceding study drug administration to 4 hours after the start of study drug administration.

13. Positive prestudy (screening) or immediate premedication blood alcohol, urine drug screen or serum pregnancy test.

20 14. Current use of tobacco products.

15. Intake of alcohol > 60 gms per day.

16. Consumption of alcoholic beverages within 48 hours of study medication application or at any time during the study.

25 17. Blood or blood products donated in the past 6 weeks prior to study medication application.

18. Positive HIV (ELISA) and/or Hepatitis B (HBsAg).

Methods

Subjects were administered BTDS 5 from day 0 to day 3, BTDS 10 from day 3 to day 6, and BTDS 20 from day 6 to day 13. After day 13, patients were monitored for an additional 4 days (day 17).

Vital signs were measured as follows:

1. 24, 12, 8, 4, 1, and 0 hrs prior to application of BTDS 5;
2. Day 0 and 3, 30 min. prior to application of BTDS 5 and 10 and 1, 2, 4, 8, 12, 20, 23, 36, 47, and 60 hr. after the application of BTDS 5 and BTDS 10;
3. Day 6, 30 min. prior to application of BTDS 20 and 1, 2, 4, 8, 12, 20, 23, 36, 47, 60, 71, 84, 95, 108, 119, 132, 143, 156 and 164 hr. after application of BTDS 20; and
4. Day 13, 0.25, 0.50, 0.75, 1, 2, 4, 8, 12, 24, 48, and 72 hr. after removal of BTDS 20.

The vital signs tested included blood pressure (subjects remained supine for 5 minutes, then had their blood pressure measured; thereafter subjects stood, and blood pressure was measured after 1 minute of standing and after 2 minutes standing) , pulse (bpm, measured 5 minutes supine, 1 minute standing, and 2 minutes standing), respiratory rate (breaths/minute) , and transcutaneous oxygen saturation (SaO₂).

Physiologic Measurements. Blood pressure (mmHg): At each scheduled assessment time, subjects remained supine for 5 minutes, then had their BP measured. Subjects then stood, and BP was measured after 1 minute of standing and after 2 minutes of standing.

Pulse (bpm): Pulse was measured at 5 minutes supine, 1 minute standing, and 2 minutes standing.

Transcutaneous oxygen saturation (SaO_2): Transcutaneous SaO_2 was measured by pulse oximetry using a fingertip sensor that quantified SaO_2 by infrared spectrophotometry.

Pharmacokinetic sampling was conducted as follows:

(1) 0, 23, 47 hr. after application of BTDS 5 and BTDS 10;

5 (2) 0, 23, 47, 71, 95, 119, and 143 hr. after application of BTDS 20; and

(3) 0.25, 0.50, 0.75, 1, 2, 4, 8, 12, 24, 48, and 72 hr. after removal of BTDS 20.

Assessment of Local Reactions at BTDS Application Sites. Assessment of skin for reactions at the BTDS application site were made before initial system application and at
10 each BTDS removal. The appearance of the skin at the BTDS application site was rated for erythema and edema using rating scales in which erythema ranged from 0 (no visible redness) to 5 (dark red discoloration of the skin) and edema varied from 0 (no visible reaction) to 5 (severe swelling extending more than 1 mm in diameter and protruding over the edges of the system).

15 **Clinical Laboratory Tests.** Laboratory tests were carried out on blood and urine samples obtained at screening and at study completion (day 15). Blood samples were analyzed for hematology and chemistry, and urinalysis assessments included color, turbidity, specific gravity, glucose, albumin, bile (urobilinogen), pH, acetone (ketone), and microscopic examination.

20 **Physical Examination and ECG.** A standard physical examination and 12-lead ECG were conducted at screening and study completion. Vital signs were taken at these times in addition to those taken for pharmacodynamic evaluation.

Buprenorphine/Norbuprenorphine Assays. The pharmacokinetic analysis included assaying plasma samples for concentrations of buprenorphine and norbuprenorphine.

25 Norbuprenorphine is the major known Phase I metabolite of buprenorphine and has lower pharmacologic activity than its parent compound.

Briefly, buprenorphine and norbuprenorphine, and the internal standards deuterated d4-buprenorphine and deuterated d9-norbuprenorphine (Radian Corporation, Austin, TX) were measured by Liquid Chromatography-Electrospray/Mass Spectrometry/Mass Spectrometry (LC-ESI/MS/MS). For general descriptions of these technologies, see Huang et al., Anal Chem 1990, 62:713A-725A.; Heel et al., Curr Ther 1979, 5:29-33.; Watson et al., 1982, 54:37-43; Adrianensen et al., Acta Anaesthesiol Belg 1985, 36:33-40; Lewis and Walter, "Buprenorphine: An Alternative Treatment For Opioid Dependence" National Institute on Drug Abuse, Monograph series; Hand et al., 1989; Tebbett, 1985; and Blom et al., 1985. Internal standards were spiked into human plasma prior to sample preparation by pipetting appropriate volumes of d4-buprenorphine/d9-norbuprenorphine solutions into human plasma treated with EDTA to prevent coagulation.

Solid Phase Extraction (SPE) was used to isolate the two compounds of interest from 0.5 mL human plasma samples. Before extraction, all patient samples, standards, and controls were thawed at 37°C, vortexed, and centrifuged at 3000 rpm for at least 15 minutes. Buffer (8mM ammonium acetate) and internal standards were added to each plasma sample, including controls and standards (*i.e.*, samples containing known amounts of buprenorphine and/or norbuprenorphine). Each sample, standard, and control was then subjected to an extraction procedure using either Packard MultiProbe IIEX (Packard, Meriden, CT.) or Tomtec Qadra (Tomtech, Hamden, CT), wherein the analytes of interest were absorbed by a stationary phase, followed by washing to remove matrix material and elution to recovery the analytes. The eluent was evaporated to dryness under a stream of nitrogen gas at 45°C, and thereafter reconstituted in 9:1 acetonitrile:ammonium acetate (8 mM).

A High Performance Liquid Chromatography (HPLC) system based on a reverse-phase SB-C18 column (2.1 mm ID x 50 mm, 5 u particle size; Hewlett-Packard, Wilmington, DE) using an acetonitrile:ammonium acetate:methanol mobile phase, was applied to separate the components in each sample prior to MS.

The MS system consisted of a Micromass Qattro LC Mass Spectrometer equipped with an ESI source (Micromass Inc., Beverly, MA) and operated in Multiple Reaction Monitoring Mode (MRM). Quantitation was performed using a calibration curve based on

the peak area ratios of buprenorphine to d4-buprenorphine, and norbuprenorphine to d9-norbuprenorphine. The transition processes from precursor or molecular ion(s) to product ion(s) were used for both analytes to enhance the selectivity and sensitivity for buprenorphine and norbuprenorphine analysis. The transitions used were 468.1 to 55.1 (for buprenorphine), 472.4 to 59.1 (for d4-buprenorphine), 414.1 to 101.0 (for norbuprenorphine), and 423.1 to 110.0 (for d9-norbuprenorphine). The exact transition of precursor to product ion can be fine-tuned based on the mass-tune report.

The Micromass MassLynx software was used to integrate the chromatographic peaks from the MS and determine the peak area ratios of buprenorphine/d4-buprenorphine and norbuprenorphine/d9-norbuprenorphine. The ratios of the areas were determined for each plasma standard, sample, and control. The standard peak area ratios were then used to prepare a calibration curve based on a weighted ($1/x^2$) linear regression. Sample and control concentrations were calculated from the regression line in pg/mL. The quantitation limit of the method was determined to be 25 pg/mL in human plasma for both analytes, with a concentration range from 25 to 600 pg/mL in human plasma.

Pharmacokinetic Metrics. The following pharmacokinetic metrics were estimated from plasma buprenorphine and plasma norbuprenorphine concentrations following treatment with BTDS:

AUC_t (pg·h/mL). The area under the plasma concentration–time course profile from time = 0 (system application) to the last quantifiable concentration was estimated using the linear trapezoidal rule as follows:

$$AUC_t = \sum_{i=1}^{n-1} \left[\frac{C_{i+1} + C_i}{2} (t_{i+1} - t_i) \right]$$

where c_i is the concentration in the i^{th} sample, t_i is the time of the i^{th} sample from dosing, and n is the number of available samples up to and including the last quantifiable concentration.

AUC_{∞} (pg·h/mL)—The area under the plasma concentration–time course profile from time = 0 (dosing) to infinity was estimated as:

$$AUC_{\infty} = AUC_t + \frac{C_t}{\lambda_z}$$

where C_t was the last quantifiable concentration and λ_z was the negative slope
5 of the apparent terminal phase of the log-transformed profile.

C_{max} (pg/mL)— Measured plasma concentrations of buprenorphine and
norbuprenorphine versus sampling time were plotted in plasma concentration-time course
profiles for each individual. The maximum concentration of each substance was taken from
each respective profile. The average maximum concentration of each substance was
10 calculated as the arithmetic mean of all individual values.

t_{max} (h)—The time from dosing to the maximum observed concentration was taken
directly from the plasma concentration-time course profile. The average time from dosing
to the maximum observed concentration was calculated as the arithmetic mean of all
individual values.

15 $t_{1/2}$ (h)—The apparent terminal half-life was estimated as follows:

$$t_{1/2} = \frac{\ln(2)}{\lambda_z}$$

wherein λ_z is the first order rate constant associated with the terminal (log-
linear) portion of the curve. This was estimated by linear regression of time versus log
concentration. The apparent terminal half-life was considered reportable if the following
20 criteria were met:

- The observed data points must be on the terminal log-linear phase.
- At least 3 data points per determination
- Coefficient of determination (R^2) > 0.85.

If the individual time-course data set failed to meet the above criteria, the $t_{1/2}$ was reported as not estimable.

Between-group comparison within each interval for average supine BP was performed using an analysis of covariance (ANCOVA) model with the average supine blood pressure as the response variable, group as predictor, and baseline average supine blood pressure as covariate. Pairwise comparisons between the 2 elderly groups and the group of young healthy subjects were also performed. All other PD variables were analyzed in the same way.

Pharmacokinetic metrics were log-transformed for analyses. For log-transformed variables, exponentiating the differences and the limits of the confidence intervals yielded corresponding mean ratio and confidence intervals in the original scale. Between-group comparison of pharmacokinetic metrics was performed using an analysis of variance (ANOVA) model. Pairwise comparisons between the 2 elderly groups and the group of young healthy subjects were performed. Statistical significance was assessed at the 5% level with no adjustment for Type I error due to multiple comparisons. Confidence intervals (90%) were estimated around ratios (elderly healthy/young healthy and elderly hypertensive/young healthy) of the least squares means of AUC_t , AUC_{∞} , and C_{max} .

Statistical Methods. Between-group comparison within each interval for average supine BP was performed using an analysis of covariance (ANCOVA) model with the average supine BP as the response variable, group as predictor, and baseline average supine BP as covariate. Pairwise comparisons between the 2 elderly groups and the group of young healthy subjects were also performed. All other PD variables were analyzed in the same way.

Pharmacokinetic metrics were log-transformed for analyses. For log-transformed variables, exponentiating the differences and the limits of the confidence intervals yielded corresponding mean ratio and confidence intervals in the original scale. Between-group comparison of pharmacokinetic metrics was performed using an analysis of variance (ANOVA) model. Pairwise comparisons between the 2 elderly groups and the group of young healthy subjects were performed. Statistical significance was assessed at the 5%

level with no adjustment for Type I error due to multiple comparisons. Confidence intervals (90%) were estimated around ratios (elderly healthy/young healthy and elderly hypertensive/young healthy) of the least squares means of AUC_t , AUC_∞ , and C_{max} .

Results and Discussion

5 ***Subject Demographics and Baseline Disposition.*** Thirty-six subjects were enrolled in the study: 12 young healthy subjects (aged 21 to 40 years, mean age 29 years), 13 elderly healthy subjects (aged 65 to 74 years, mean age 68 years), and 11 elderly subjects with hypertension (aged 65 to 80 years, mean age 71 years). All subjects were evaluable for pharmacodynamic and safety assessments, and 32 provided data for pharmacokinetic
10 analysis. Demographic and baseline physiologic characteristics for the subjects are summarized in Table 1.

TABLE 1

Baseline demographic characteristics and hemodynamic and
respiratory parameters for the 3 subject groups

	Young Healthy (n = 12)	Elderly Healthy (n = 13)	Elderly Hypertensive (n = 11)
Mean age (yrs; (range))	29 (21-40)	68 (65-74)	71 (65-80)
Weight (kg; (range))	72 (50-93)	74 (50-85)	75 (57-91)
Gender (%)			
Male	10 (83%)	8 (62%)	3 (27%)
Female	2 (17%)	5 (38%)	8 (73%)
Race (%)			
White	9 (75%)	12 (92%)	10 (91%)
Hispanic	2 (17%)	1 (8%)	1 (9%)
Other	1 (8%)	0	0
Mean (SE) blood pressure (mm Hg)			
5-minute supine			
Systolic	114.7 (2.6)	128.7 (4.5)	128.2 (3.1)
Diastolic	67.9 (1.9)	75.3 (1.9)	71.6 (1.4)
2-minute standing			
Systolic	116.3 (3.0)	129.7 (3.6)	132.5 (3.5)
Diastolic	74.9 (2.1)	79.4 (2.6)	82.7 (2.9)
Mean (SE) pulse (bpm)			
5-minute supine	57.2 (2.3)	66.1 (2.6)	65.8 (2.8)
2-minute standing	73.8 (2.9)	78.3 (3.2)	78.3 (3.2)
Mean (SE) RR (breaths/min)	15.5 (1.0)	13.2 (0.5)	12.9 (0.6)
Mean (SE) %SaO ₂	95.4 (0.6)	93.4 (1.3)	93.9 (0.7)

Respiratory Rate and Oxygen Saturation. Table 2 summarizes data for RR and

5 %SaO₂ at baseline, at 6 to 8 hours following application of each BTDS, and 4 hours after removal of BTDS 20. In all groups, changes in mean RR were small. At baseline, mean %SaO₂ in the 2 elderly groups was slightly below the reference range. Compared to baseline, mean %SaO₂ values at each assessment did not change significantly in any of the 3 groups. No respiratory depression was observed.

TABLE 2Changes from baseline^a in RR and oxygen saturation (%SaO₂) with application of BTDS^b

	Mean Change (SE)		
	Young Healthy	Elderly Healthy	Elderly Hypertensive
	(n = 12)	(n = 13)	(n = 11)
Respiratory rate (breaths/min)			
Baseline	15.50 (0.96)	13.17 (0.52)	12.91 (0.62)
Change from baseline to:			
Application 1 (BTDS 5), Day 0 (8h)	-1.00 (1.49)	1.00 (1.19)	0.45 (0.95)
Application 2 (BTDS 10), Day 3 (80h)	-1.67 (1.10)	1.50 (0.86)	0.55 (1.08)
Application 3 (BTDS 20), Day 6 (148h)	-2.91 (1.09) ^c	0.83 (0.87)	0.09 (0.64)
After BTDS 20 removal, Day 13 (315.5h)	-0.55 (0.94) ^c	0.00 (0.66) ^d	1.27 (0.86)
%SaO ₂ ^e			
Baseline	95.42 (0.62)	93.38 (1.32)	93.91 (0.65)
Change from baseline to:			
Application 1 (BTDS 5), Day 0 (8h)	0.42 (0.88)	1.00 (1.63)	-0.36 (0.59)
Application 2 (BTDS 10), Day 3 (80h)	-0.17 (0.76)	0.77 (1.14)	-0.27 (0.75)
Application 3 (BTDS 20), Day 6 (148h)	-0.36 (0.92) ^c	2.15 (1.27)	2.00 (0.69)
After BTDS 20 removal, Day 13 (315.5h)	-0.64 (0.99) ^c	0.58 (1.54) ^f	-0.64 (1.03)

^aChange is from pre-BTDS (0.5 hour) to postapplication; mean change is the change for each subject averaged for the entire group at the specified assessment time.

5 ^bAssessment intervals were 6 to 8 hours following each BTDS application and 4 hours after BTDS removal.

^cEleven young healthy subjects were evaluable for RR and %SaO₂ after application 3 and BTDS 20 removal.

^dEleven elderly healthy subjects were evaluable for RR after BTDS 20 removal.

^eReference range: 95% to 110%.

^fTwelve elderly healthy subjects were evaluable for %SaO₂ after BTDS 20 removal.

10 **Pharmacokinetics.** Plasma concentration versus time curves for the 3 groups for
buprenorphine and its metabolite, norbuprenorphine, are shown in Figures 1 and 2,
respectively; pharmacokinetic parameters are summarized in Table 3. There were no
statistically significant differences between groups for any of the buprenorphine or
norbuprenorphine pharmacokinetic parameters evaluated. The AUC_t and C_{max} for
15 norbuprenorphine were higher in the elderly with hypertension than in the elderly healthy
or the young healthy subjects.

TABLE 3

Pharmacokinetic parameters for buprenorphine and norbuprenorphine
after application of BTDS 20

	Mean (SE)		
	Young Healthy (n = 11)	Elderly Healthy (n = 10)	Elderly Hypertensive (n = 11)
Buprenorphine			
AUC _t (pg·h/mL)	86026 (7808)	78674 (7707)	94022 (4242)
AUC _∞ (pg·h/mL)	87485 (8867) ^a	81129 (8034)	99087 (4481)
C _{max} (pg/mL)	722 (82)	562 (78)	610 (58)
t _{max} (h)	178 (5)	181 (6)	208 (13)
t _{1/2} (h)	29 (3) ^a	33 (4)	42 (2)
Norbuprenorphine			
AUC _t (pg·h/mL)	31359 (3447)	26210 (3102)	37695 (4023)
AUC _∞ (pg·h/mL)	33535 (3945) ^a	30913 (3976) ^b	□ ^c
C _{max} (pg/mL)	191 (21)	158 (18)	260 (40)
t _{max} (h)	240 (16)	257 (14)	295 (13)
t _{1/2} (h)	45 (7) ^a	48 (5) ^b	□ ^c

^aTen young healthy subjects were evaluable for AUC_∞ and t_{1/2}.

5 ^bSeven elderly healthy subjects were evaluable for AUC_∞ and t_{1/2}.

^cFour elderly subjects with hypertension were evaluable for AUC_∞ and t_{1/2} because for 7 subjects in this group, norbuprenorphine concentrations remained high at the final measurement (72 hours after removal of last BTDS).

Safety

10 **Adverse Events.** All subjects tolerated BTDS well. Adverse events reported by more than one subject in any treatment group are summarized in Table 4. Two severe, treatment-related adverse events (cholecystitis and abdominal pain, recorded for the same young adult subject) required hospitalization. Two subjects discontinued due to treatment-related adverse events: one young adult subject discontinued on study day 5 due to vomiting
15 and one elderly healthy subject discontinued due to low blood pressure experienced on day 10. These adverse events resolved prior to discharge from the facility.

TABLE 4

Incidence of subjects with clinical adverse events reported by more than 1 subject in
at least one of the groups

	Young Healthy (n = 12)	Elderly Healthy (n = 13)	Elderly Hypertensive (n = 11)	Total (n = 36)
	Subjects n (%)			
Dizziness	8 (67)	8 (62)	3 (27)	19 (53)
Constipation	7 (58)	7 (54)	3 (27)	17 (47)
Abdominal pain	3 (25)	6 (46)	6 (55)	15 (42)
Nausea	6 (50)	2 (15)	5 (46)	13 (36)
Vomiting	4 (33)	2 (15)	4 (36)	10 (28)
Vasodilation	4 (33)	1 (8)	1 (9)	6 (17)
Headache	5 (42)	1 (8)	0	6 (17)
Sweating	1 (8)	1 (8)	4 (36)	6 (17)
Pain	4 (33)	0	1 (9)	5 (14)
Pruritus at site	2 (17)	1 (8)	2 (18)	5 (14)
Dry mouth	1 (8)	1 (8)	3 (27)	5 (14)
Back pain	3 (25)	0	2 (18)	5 (14)
Pruritus	1 (8)	1 (8)	2 (18)	4 (11)
Asthenia	4 (33)	0	0	4 (11)
Dyspepsia	0	0	4 (36)	4 (11)
Chills	3 (25)	0	1 (9)	4 (11)
Nervousness	2 (17)	1 (8)	1 (9)	4 (11)
Pharyngitis	2 (17)	2 (15)	0	4 (11)

Application Site Reactions. Application site erythema and edema for each BTDS

- 5 dose are summarized in Table 5. Most of the subjects experienced mild application site reactions. None of the reports of erythema or edema were severe or dose limiting.

TABLE 5

Application site erythema and edema at baseline and after removal of BTDS 5, 10, and 20

	Young Healthy	Elderly Healthy	Elderly Hypertensive
	(n = 12)	(n = 13)	(n = 11)
	Subjects n (%)		
Erythema			
Day 0 (predose)			
No visible redness	12 (100)	13 (100)	11 (100)
Day 3 (BTDS 5 removal)			
No visible redness	0	8 (62)	2 (18)
Very slight redness	12 (100)	4 (31)	9 (82)
Slight but well-defined	0	1 (8)	0
redness			
Moderately intense redness	0	0	0
Day 6 (BTDS 10 removal)			
No visible redness	0	2 (15)	0
Very slight redness	6 (50)	8 (62)	10 (91)
Slight but well-defined	5 (42)	3 (23)	1 (9)
redness			
Moderately intense redness	0	0	0
Day 13 (BTDS 20 removal)			
No visible redness	1 (8)	2 (15)	0
Very slight redness	4 (33)	8 (62)	6 (55)
Slight but well-defined	7 (58)	3 (23)	2 (18)
redness			
Moderately intense redness	0	0	3 (27)
Edema			
Day 0 (baseline)			
No visible reactions	12 (100)	13 (100)	11 (100)
Very mild edema	0	0	0
Mild edema	0	0	0
Moderate edema	0	0	0
Day 3 (BTDS 5 removal)			
No visible reactions	11 (92)	12 (92)	9 (82)
Very mild edema	1 (8)	1 (8)	2 (18)
Mild edema	0	0	0
Moderate edema	0	0	0

Day 6 (BTDS 10 removal)			
No visible reactions	11 (92)	12 (92)	6 (55)
Very mild edema	0	1 (8)	4 (36)
Mild edema	0	0	1 (9)
Moderate edema	0	0	0
Day 13 (BTDS 20 removal)			
No visible reactions	12 (100)	13 (100)	6 (55)
Very mild edema	0	0	2 (18)
Mild edema	0	0	2 (18)
Moderate edema	0	0	1 (9)

Physical Examination, Laboratory Tests, or ECG. There were no clinically significant changes in physical examination, laboratory test, or ECG results.

The pharmacokinetic analysis showed that there were no potentially confounding differences between the pharmacokinetics of BTDS in elderly versus young healthy subjects (Figures 1 and 2). The results of this pharmacokinetic study showed that BTDS was well-tolerated, even with the high doses achieved. These data provide the rationale for starting dosing with BTDS 5, the lowest dose, and increase dosing after 3 days of wear.

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The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims. It is further to be understood that values are approximate, and are provided for description.

Patents, patent applications, publications, procedures, and the like are cited throughout this application, the disclosures of which are incorporated herein by reference in their entireties for all purposes.

WHAT IS CLAIMED IS:

1. A method of reducing the incidence of breakthrough symptoms in a patient suffering from diarrhea, which method comprises:

administering to a patient in need of such treatment a first buprenorphine-
5 containing transdermal dosage form for a first dosing period that is no longer than about 7 days;

at the end of the first dosing period, administering to the patient a second buprenorphine-containing transdermal dosage form for a second dosing period that is no longer than about 5 days, wherein the second dosage form comprises the same dosage of
10 buprenorphine as, or a greater dosage of buprenorphine than, the first dosage form; and

at the end of the second dosing period, administering to the patient a third buprenorphine-containing transdermal dosage form for a third dosing period, wherein the third dosage form comprises a greater dosage of buprenorphine than the second dosage form.

15 2. The method of claim 1, wherein the first, second, and third transdermal dosage forms contain the amounts of buprenorphine as set forth in a row of the following table:

First (mg)	Second (mg)	Third (mg)
5	5	10
5	5	20
5	5	30
5	10	20
5	10	30
5	10	40
5	20	40
5	30	40
10	10	20
10	10	30
10	10	40
10	20	30

10	20	40
10	30	40
20	20	30
20	30	40

3. The method of claim 1, wherein the first dosing period is at least about 2 days.

4. The method of claim 1, wherein the second dosing period is at least about 2 days.

5 5. The method of claim 1 wherein the third dosing period is at least about 2 days.

6. The method of claim 1 wherein the first dosage form comprises 5 mg of buprenorphine.

10 7. The method of claim 1 wherein the second dosage form comprises 10 mg of buprenorphine.

8. The method of claim 1 wherein the third dosage form comprises 20 mg of buprenorphine.

9. The method of claim 1, wherein the third dosage form comprises 30 mg of buprenorphine.

15 10. The method of claim 1, wherein the third dosage form comprises 40 mg of buprenorphine.

11. The method of claim 1, wherein the administration of the third dosage form is repeated at least once.

20 12. The method of claim 11, wherein the dosing period for the repeated administration of the third dosage form is at least 2 days.

13. The method of claim 11, wherein the third dosage form comprises 30 or 40 mg of buprenorphine.

14. The method of claim 1, wherein the breakthrough symptom is a member of the group consisting of abnormally loose or liquid feces, abnormally frequent emptying of
5 bowels, and cramping abdominal pain.

15. The method of claim 1 wherein the patient has irritable bowel syndrome.

16. The method of claim 1 wherein the patient has short gut syndrome.

17. The method of claim 1 wherein the patient has microscopic colitis.

18. The method of claim 1 wherein the patient has a carcinoid tumor secreting
10 vasoactive intestinal peptide (VIP).

19. The method of claim 1, wherein the first dosage form comprises up to 5 mg of buprenorphine, and the first dosing period is up to 3 days; the second dosage form comprises up to 5 mg of buprenorphine and the second dosing period is up to 3 days; and the third dosage form comprises up to 20 mg of buprenorphine and the third dosing period
15 at least about 7 days.

20. The method of claim 1, wherein the transdermal dosage form is selected from a transdermal dosage article and a transdermal dosage composition.

21. The method of claim 20, wherein the transdermal dosage article is a diffusion-driven transdermal system.

22. The method of claim 20, wherein the transdermal dosage composition is selected from the group consisting of a topical gel, a lotion, an ointment, a transmucosal system, a transmucosal device, and an iontophoretic delivery system.

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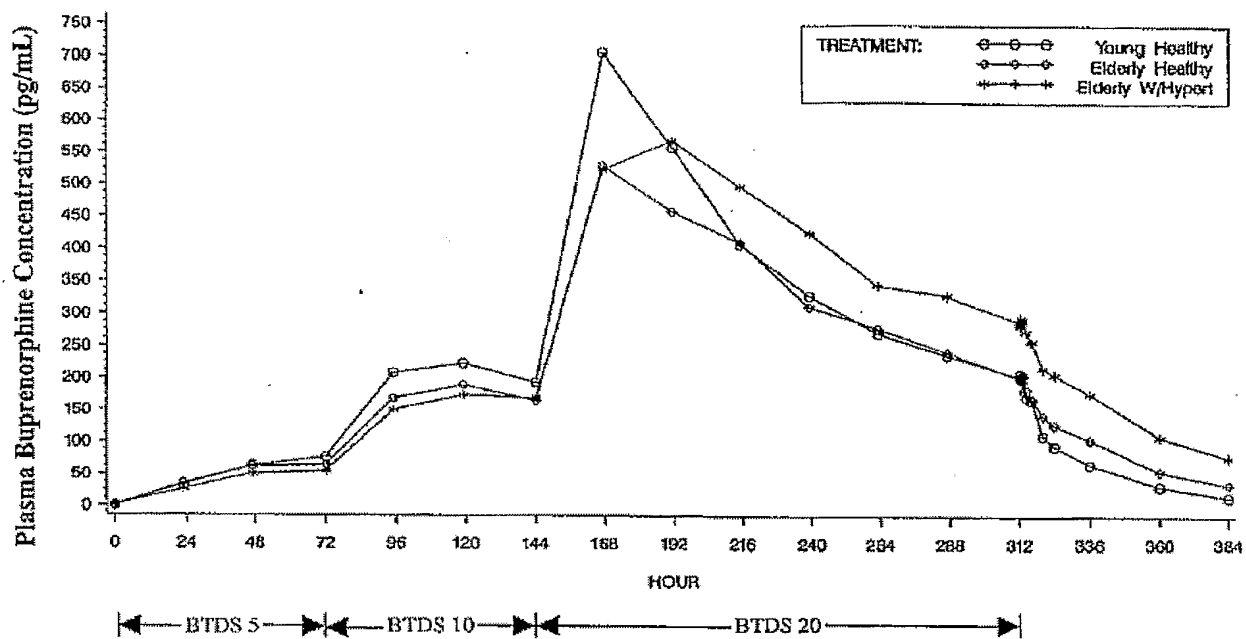


FIGURE 1

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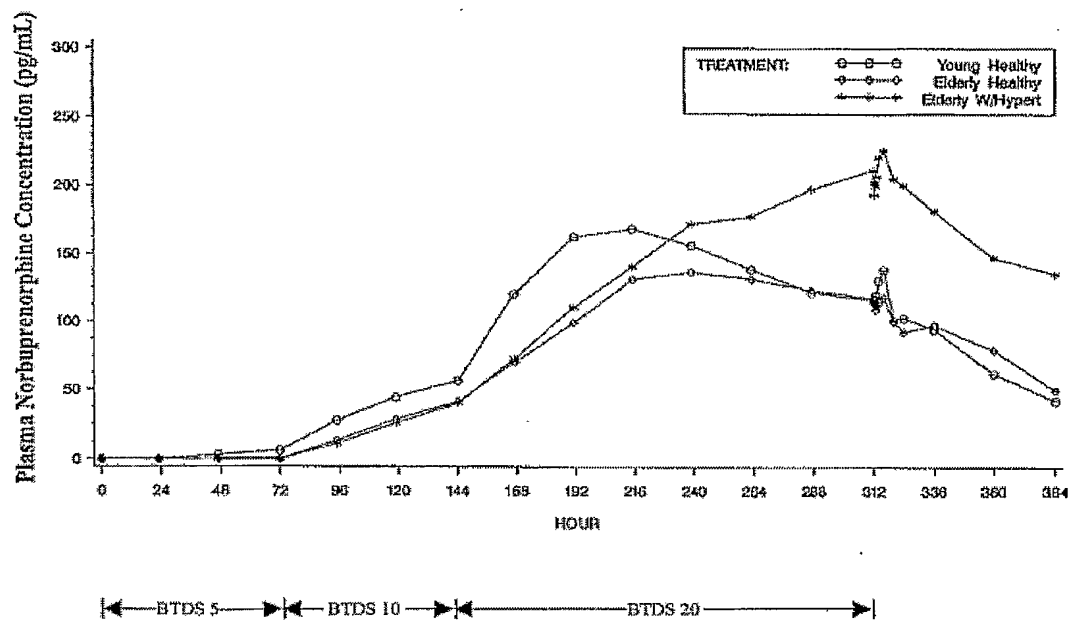


FIGURE 2